Application No. 10/686,809 Docket No.: ZIPH-009-102 Amendment dated August 22, 2007

After Final Office Action of June 22, 2007

## **AMENDMENTS TO THE CLAIMS**

## 1-13. (Cancelled).

14. (Currently Amended) A method of treating multidrug-resistant tumors or inhibiting angiogenesis or metastasis, comprising administering to a patient in need thereof, an amount of one or more N-substituted indol-3-glyoxylamides of formula I or a physiologically tolerable acid addition salt thereof effective for treating multidrug-resistant tumors or inhibiting angiogenesis or metastasis

$$R_4$$
 $R_3$ 
 $R_2$ 
 $R_1$ 
 $R_1$ 
 $R_2$ 
 $R_1$ 
 $R_1$ 
 $R_2$ 
 $R_1$ 

wherein the radicals R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and Z have the following meanings:

R is hydrogen; (C<sub>4</sub>-C<sub>6</sub>) alkyl, where the alkyl group is optionally mono- or polysubstituted by a phenyl ring wherein the phenyl ring is optionally substituted by one or more substituents selected from halogen, (C<sub>4</sub>-C<sub>6</sub>) alkyl, (C<sub>3</sub>-C<sub>7</sub>) cycloalkyl, a carboxyl group, a carboxyl group esterified with a C<sub>4</sub>-C<sub>6</sub>-alkanol, a trifluoromethyl group, a hydroxyl group, a methoxy group, an ethoxy group, a benzyloxy group or a benzyl group which is mono- or polysubstituted on the phenyl moiety by a (C<sub>4</sub>-C<sub>6</sub>) alkyl group, a halogen and a trifluoromethyl group, or

R is a tert-butoxycarbonyl radical[[,]] or an acetyl group,

R<sub>1</sub> is a phenyl ring, which is optionally substituted by one or more substituents selected from (C<sub>4</sub>-C<sub>6</sub>) alkyl, (C<sub>4</sub>-C<sub>6</sub>) alkoxy, eyano, halogen, trifluoromethyl, hydroxyl, benzyloxy, nitro, amino, (C<sub>4</sub>-C<sub>6</sub>) alkylamino, (C<sub>4</sub>-C<sub>6</sub>) alkoxycarbonylamino, a carboxyl group, a carboxyl group esterified with and C<sub>4</sub>-C<sub>6</sub> alkanol; or R<sub>4</sub> is a pyridine structure of formula II

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$$R_5$$
  $4$   $3$   $2$   $R_6$  (II)

where the pyridine structure is bonded at either the 2, 3, or 4 position of the ring and is optionally substituted by substituents R<sub>5</sub> or R<sub>6</sub> or both R<sub>5</sub> and R<sub>6</sub>, and wherein R<sub>5</sub> and R<sub>6</sub> can be identical or different and are independently selected from (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, nitro, amino, hydroxyl, halogen, trifluoromethyl, ethoxycarbonylamino radical and a carboxyalkyloxy group in which the alkyl group has 1-4 C atoms, or

R<sub>1</sub> is a 2- or 4-pyrimidinyl heterocycle where the 2-pyrimidinyl ring can be mono-or polysubstituted by a methyl group; a 2-, 3-, 4-, or 8-quinolyl, wherein the quinolyl structure is optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)-alkyl, halogen, a nitro group, an amino group, and a (C<sub>1</sub>-C<sub>6</sub>)-alkylamino radical; a 2-, 3-, or 4-quinolylmethyl, where the ring carbons of the pyridylmethyl radical of the quinolyl group and of the quinolylmethyl radical are optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, nitro, amino, and (C<sub>1</sub>-C<sub>6</sub>)-alkoxycarbonylamino, or

R<sub>1</sub>, in the case in which R is hydrogen, a methyl group, a benzyl group, a benzyloxycarbonyl radical, a tert-butoxycarbonyl radical, or an acetyl group, can further be a radical selected from -CH<sub>2</sub>COOH; -CH(CH<sub>3</sub>)-COOH; (CH<sub>3</sub>)<sub>2</sub>-CH-(CH<sub>2</sub>)<sub>2</sub>-CH-COO-; H<sub>3</sub>C-H<sub>2</sub>C-CH(CH<sub>3</sub>)-CH(COOH) ; HO-H<sub>2</sub>C-CH(COOH) ; phenyl-CH<sub>2</sub>CH(COOH) ; (4-imidazolyl) CH<sub>2</sub>-CH-(COOH) ; HN=C(NH<sub>2</sub>)-NH-(CH<sub>2</sub>)<sub>3</sub>-CH(COOH) ; H<sub>2</sub>N-(CH<sub>2</sub>)<sub>4</sub>-CH(COOH) ; H<sub>2</sub>N-CO-CH<sub>2</sub>-CH-(COOH) ; and HOOC-(CH<sub>2</sub>)<sub>2</sub>-CH(COOH) ; or

R<sub>I</sub>, in the case in which R is hydrogen, a benzyloxycarbonyl radical, a tert-butoxycarbonyl radical, an acetyl group, or a benzyl group, can further be an acid radical of a natural or unnatural amino-acid, or

R<sub>1</sub> can be an alkylamino-carbonyl-2-methylprop-1-yl-group;

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R and R<sub>1</sub> can further form, together with the nitrogen atom to which they are bonded, the structure of formula 3

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wherein R<sub>7</sub> is an alkyl radical, a benzhydryl group, a bis-p-fluorobenzhydryl group, or a phenyl ring it can be mono- or polysubstituted by (C<sub>1</sub>-C<sub>6</sub>) alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkoxy, halogen, a nitro group, an amino group or a (C<sub>1</sub>-C<sub>6</sub>) alkylamino group;

- R<sub>2</sub> is a hydrogen or a (C<sub>1</sub>-C<sub>6</sub>)-alkyl group, where the alkyl group is mono<u>substituted</u>—or polysubstituted by halogen or phenyl, which is optionally substituted by one or more substituents selected from halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, a carboxyl group, a carboxyl group esterified with a C<sub>1</sub>-C<sub>6</sub>-alkanol, a trifluoromethyl group, a hydroxyl group, a methoxy group, an ethoxy group a benzyloxy group, a 2-quinolyl group or a 2-, 3- or 4-pyridyl group, wherein the 2-quinolyl and 2-, 3-, or 4-pyridyl groups can both in each case be mono- or polysubstituted by halogen, (C<sub>1</sub>-C<sub>4</sub>)-alkyl group or (C<sub>1</sub>-C<sub>4</sub>)-alkoxy<sub>5</sub>-or
- R<sub>2</sub> is an aroyl radical, where the aryl-moiety on which this radical is based is a phenyl ring, which is optionally substituted by one or more substituents selected from halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, a carboxyl group, a carboxyl group esterified with a C<sub>1</sub>-C<sub>6</sub>-alkanol, a trifluoromethyl group, a hydroxyl group, a methoxy group, an ethoxy group or a benzyloxy group;
- R<sub>3</sub> and R<sub>4</sub> can be identical or different and are independently selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, halogen, and benzyloxy, or a nitro group, an amino group, a (C<sub>1</sub>-C<sub>4</sub>)-mono or dialkyl-substituted amino group, a (C<sub>1</sub>-C<sub>6</sub>) alkoxycarbonylamino group, or and a (C<sub>1</sub>-C<sub>6</sub>)-alkoxycarbonylamino-(C<sub>1</sub>-C<sub>6</sub>)-alkyl group; and

Z is O or S.

15-17. (Cancelled).

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18. (Currently Amended) The method of claim 14, wherein R is hydrogen; R<sub>1</sub> is 4-pyridyl-or 4-fluorophenyl; R<sub>2</sub> is benzyl, 4-chlorobenzyl, 4-fluorobenzyl, 3-pyridylmethyl, 4-bromobenzyl; R<sub>3</sub> and R<sub>4</sub> are hydrogen; and Z is oxygen.

- 19. (Currently Amended) The method of claim 14, wherein one or more of the N-substituted indol-3-glyoxylamides are selected from N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl] glyoxylamide; N-(pyridin-4-yl)-(1-benzylindol-3-yl) glyoxylamide; N-(4-fluorobenzyl)indol-3-yl] glyoxylamide; N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl] glyoxylamide; N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl] glyoxylamide, and their physiologically tolerable acid-addition salts.
- 20. (Currently Amended) The method according to claim 14, wherein the acid addition salt is a salt of a mineral acid or a salt of an organic acid.
- 21. (Previously Presented) The method according to claim 20, wherein the salt of the mineral acid is selected from hydrochloric acid, sulfuric acid, and phosphoric acid, and the salts or organic acids are selected from acetic acid, lactic acid, malonic acid, maleic acid, fumaric acid, gluconic acid, glucuronic acid, citric acid, embonic acid, methanesulfonic acid, trifluoroacetic acid, succinic acid, and 2-hydroxyethanesulfonic acid.
  - 22. (Cancelled).
- 23. (Previously Presented) The method according to claim 14, wherein the multidrug-resistant tumor is at least resistant to an antitumor drug selected from taxol, doxorubicin, vincristine, and epothilone B.
- 24. (Currently Amended) The method according to claim 14, wherein the one or more N-substituted indol-3-glyoxylamides are used by themselves, in combination with one or more known antitumor agents, or as a replacement therapy for tumors resistant to one or more known antitumor agents—which are no longer active on account of resistance formation.

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25. (Previously Presented) The method of claim 24, wherein the antitumor agent used in combination with the one or more N-substituted indol-3-glyoxylamides is selected from taxol, doxorubicin, vincristine, and epothilone B.

- 26. (Previously Presented) The method of claim 24, wherein the antitumor agent for replacement by one or more N-substituted indol-3-glyoxylamides is selected from taxol, doxorubicin, vincristine, and epothilone B.
- 27. (Currently Amended) The method according to claim 25, wherein the one or more N-substituted indol-3-glyoxylamides and the one or more antitumor agents are combined together with further comprise a pharmaceutically utilizable vehicle, diluent, or excipient.
- 28. (Currently Amended) The method according to claim 27, wherein the one or more N-substituted indol-3-glyoxylamides, the one or more antitumor agents, and the pharmaceutically utilizable vehicle, diluent, or excipient is in the form of are formulated as a tablet, coated tablet, capsule, solution for infusion, or ampoule, suppository, patch, powder preparation suitable for which can be employed by inhalation, suspension, cream or ointment.
- 29. (Currently Amended) The method of claim 26, wherein the N-substituted indol-3-glyoxylamide is selected from N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl] glyoxylamide; N-(pyridin-4-yl)-(1-benzylindol-3-yl) glyoxylamide; N-(4-fluorobenzyl)-[1-(3-pyridylmethyl)indol-3-yl] glyoxylamide; N-(pyridin-4-yl)-[1-(4-chlorobenzyl)indol-3-yl] glyoxylamide; N-(pyridin-4-yl)-[1-(4-fluorobenzyl)indol-3-yl] glyoxylamide, or aphysiologically tolerable acid-addition salt thereof.
- 30. (Previously Presented) The method of claim 14, wherein the N-substituted indol-3-glyoxylamide is N-(pyridin-4-yl)-[1-(4-chlorobenzyl)indol-3-yl] glyoxylamide or a physiologically tolerable acid-addition salt thereof.

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